AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: 24741-1521

Applicant(s) Bernd GRONER *et al.*

Appl. No.: 09/596,774 Examiner: K. Canella

Filing Date: June 19, 2000 Art Unit: 1642

Title: BIFUNCTIONAL PROTEIN, PREPARATION AND USE

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10/8/02

Request for Reconsideration under 37 C.F.R. §1.116

Commissioner for Patents
ATTN: BOX AF
Washington, D.C. 20231

Ok to enter -KAC

Sir:

Applicants herein respond to the Final Office Action mailed July 30, 2002 (Paper No. 14). As this reply is being filed within two months of the mailing date of the Final Office Action, Applicants believe that no fee is due. Please debit any underpayments, or credit any overpayments, to firm deposit account no. 08-1641.

REMARKS

Claims 2-7, 9-11, 13 and 15 are pending. The office action is addressed below.

35 USC §103(a) - Obviousness

The Examiner maintains rejection of claims 2-7, 9-11, 13 and 15 under 35 USC §103(a) as allegedly obvious over Stancovski et al, (Journal of Immunology, 1993, Vol. 11, pp. 6577-6582) in view of Brocker et al (Eur. J. Immunology, 1993, Vol. 23, pp. 1435-1439, reference AA of the IDS filed 9/22/00) and Horgan et al (Journal of Immunology, 1993, Vol. 150, pp. 5400-5407).

At the outset, applicants note that the examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that it is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001). Thus, the examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986).

The Examiner asserts that Stancovski et al is "silent with respect to the presence or absence of a hinge region in the bifunctional protein" and that Horgan et al teach the enhanced affinity of chimeric antibodies containing hinge regions versus those with deleted hinge regions. The Examiner concludes that it would have been obvious, and one of skill in the art would be motivated, to make the antibody of Stancovski with a hinge region in order to attain enhanced binding affinity of the bifunctional antibody.

Applicants respectfully disagree. First, the presence or absence of a hinge region is not ambiguous in Stancovski. No hinge is discussed, because there is no hinge. The text very clearly states, "[t]he combination of the scFv...with the...ζ-subunits...in a continuous polypeptide resulted in a functional receptor..." (Stancovski page 6577, right column). Had a hinge region been interposed between the scFv portion and the ζ-subunit portion of the "continuous polypeptide," surely it would have been disclosed here. Rather, Stancovski et al disclosed chimeric molecules that were functional without a hinge region. The skilled person would have concluded from Stancovski et al that there was no need to use a hinge region. This conclusion would be further supported by US Patents No. 5,571,894 and 5,939,531, which disclose that the scFv(FRP5)-ETA antibody toxin is functional without a hinge region. In contrast, it has been surprisingly found, in the present invention, that the bifunctional construct comprising the FRP5 antibody domain in combination with the ζ-chain domain is only functional with a hinge region.

Second, Horgan et al disclose that intact IgG1 bound free peptide better than did hinge deleted IgG1. However, binding of CYYYEEEEY-BSA by hinge-deleted and intact IgG1 was similar. Further, hinge-deleted IgG4 showed better binding than did intact IgG4. Therefore, there is no general teaching that the presence of a hinge region improves binding even within a class of antibodies, much less within an artificial construct comprising an antigen binding domain derived from an anti-ERbB2 antibody and a ζ-signal-transducing subunit of the TCR/CD3 complex. Even if such teaching could be derived from Horgan et al, the skilled person would not have been motivated to combine Horgan et al with Stancovski et al, since there seemed to be no need to improve the binding of the chimeric molecules of Stancovski et al. These molecules already appeared to be functional. The assumption that the binding of immunoglobulins to peptides might be improved by a hinge region does not lead to the conclusion that bifunctional constructs with a hinge region are functional in targeting tumor cells. Therefore, the skilled person had no reasonable expectation of success in arriving at the claimed invention by any combination of the cited prior art.

Accordingly, Applicants only can conclude that the Examiner impermissibly has engaged in "hindsight" reconstruction by using Applicants' teaching as a blueprint to hunt through the

prior art for the claimed elements and combine them as claimed. *In re Zurko*, 111 F.3d 8876, 42 USPQ2d 1476 (Fed. Cir. 1997); *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ2D 1551, 1554 (Fed. Cir. 1996). Therefore, the obviousness rejection should be withdrawn.

The above rejections call to mind the following instructions from the Federal Circuit:

> virtually all inventions are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.
>
> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. (emphasis added).

Yamanouchi Pharma. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (*citing In re Rouffet,* 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). In the instant case, the Examiner has failed to identify a suggestion or motivation to combine the claim elements in a manner so as to have a reasonable expectation of success in creating the claimed invention.

CONCLUSION

In view of the above arguments, Applicants respectfully request the withdrawal of the rejection of the pending claims under 35 U.S.C. §103(a) and that the case be passed to allowance.

Respectfully submitted,

Date: September 25, 2002

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